



Attorney Docket No. UAB-17404/22

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Fengxia Qi et al.

Serial No.: 10/790,914

Group Art Unit: 1645

Filing Date: March 2, 2004

Examiner: Vanessa L. Ford

For: NOVEL LANTHIONINE ANTIBIOTIC COMPOSITIONS AND METHODS

DECLARATION OF PAGE W. CAUFIELD, DDS, PhD

I, Page W. Caufield, declare as follows:

1. I am professor and head of the Division of Diagnostics, Infectious Disease and Health Promotion in the Department of Cariology and Operative Dentistry at the College of Dentistry, New York University, in New York City, New York. Previously I was a professor in the College of Dentistry and the University of Alabama at Birmingham, Birmingham, Alabama.

2. I earned a DDS degree from Case Western Reserve University in 1973. From 1973 to 1977 I held a post-doctoral position in microbiology with a specialty in pediatric dentistry at Harvard University, Harvard Schools of Medicine, School of Dental Medicine and Forsyth Dental Center. Thereafter I completed post-doctoral studies in molecular genetics at the University of Michigan and earned a Ph.D. degree in cellular and molecular biology from the University of Alabama at Birmingham, Alabama, in 1990. Over the past fifteen years I have studied antimicrobial approaches to dental caries management and in particular mutacin proteins as possible therapeutics for the treatment of dental caries and other bacterial infections. I have authored or coauthored over 150 scientific publications in the field.

3. I am a coinventor on the above-identified patent application, U.S. Patent Application Serial No. 10/790,914 ("the application") and have read the Office Action dated October 19, 2005 ("the Office Action"). I have also reviewed and am familiar with the Loyola-Rodriguez et al., J. Genl. Microbiology (1992), 138, 269-274; and the work of my colleague Shigeyuki Hamada.

4. I understand that claims 9 and 10 of the application have been rejected under 35 U.S.C. §102(b) as anticipated by the Loyola-Rodriguez et al. reference. I understand the rejection to be that mutacin I is considered to be inherent within this reference. I state as a worker in the field, and colleague of Dr. Hamada that mutacin I is not equivalent to mutacin MT6223. My statement is based on the information found below in paragraph 8.

5. I understand that claims 9-22 of the application have been rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the treatment of infections associated with gram-positive bacteria. It is my opinion that inhibition zone studies I have conducted with mutacin I indicate this peptide to be effective against a variety of pathogenic gram-positive bacteria including multiple drug resistant *Staphylococcus*, vancomycin-resistant *Enterococcus*, anthrax, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. My opinion is based on the inhibition zone studies provided and my familiarity with the subject matter. Based on the broad spectrum of mutacin I to inhibit pathogenic gram-positive bacteria, I believe that one of my colleagues of skill in the field would have little difficulty in using or testing the efficacy of mutacin I against a Gram positive bacterial target; especially since the mutacin I operon (SEQ ID No: 3) is available from GenBank (Accession No. AF207710). Furthermore, upon isolation and purification of mutacin I through conventional technique, the delivery of mutacin I to a subject

through standard administration routes is easily accomplished. Likewise, performing inhibition zone testing of mutacin I is routine procedure in my laboratory and that of my peers.

6. To test the ability of mutacin I to function as an antibiotic, stab tests of culture media growing various pathogenic organisms were performed. These stab tests were performed according to the procedures detailed in the patent application. The original photographs showing the zone of inhibition are provided as an appendix for *Streptococcus pyogenes*, *Streptococcus pneumoniae*, multiple drug resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* bacteria. Mutacin I proved highly effective against streptococci, effective against vancomycin-resistant *Enterococcus*, and of varying efficacy against multiple resistant *Staph aureus* depending on concentration and the purity of the preparation. Additionally, semi-purified mutacin I, II and III were found effective on an overlayer of *Bacillus anthracis* Sterne with the inhibition zones depicted in the image bounded by dark line border are those corresponding to mutacin I as denoted in the attached Appendix A. The efficacy of mutacin I against anthrax is consistent with the nearest non-mutans neighbor of mutacin I being NCBI GenBank accession YP_029867 obtained from *Bacillus anthracis* Sterne.

7. In view of this data, I believe the Examiner's concerns about the breadth of the claims relative to the efficacy of mutacin I in inhibiting the broad spectrum of gram-positive bacteria have been addressed.

8. My review of Loyola-Rodriguez et al. and my familiarity with the research of Dr. Hamada leads me to the inescapable conclusion that MT6223 is in no way equivalent to mutacin I. Some notable indicators as to this dis-similarity include MT6223 being isolated from *Streptococcus sobrinus* while mutacin I is isolated from *Streptococcus mutans*. Mutacin I is single unit functional protein not known to associate with other proteins to form an active

complex. The molecular weight difference of over 4000 Daltons also makes clear to me that MT6223 is a wholly distinct protein from mutacin I. Thus, I see no teaching in the Loyola-Rodriguez et al. reference that is relevant to the invention my coinventors and I are claiming in claims 9 and 10.

9. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. These statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

/Page W. Caufield/

Page W. Caufield

Date: January 17, 2006

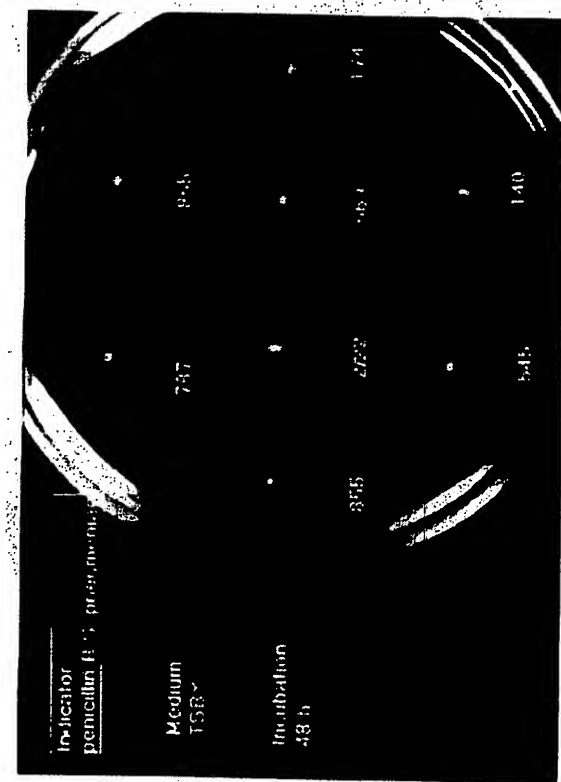
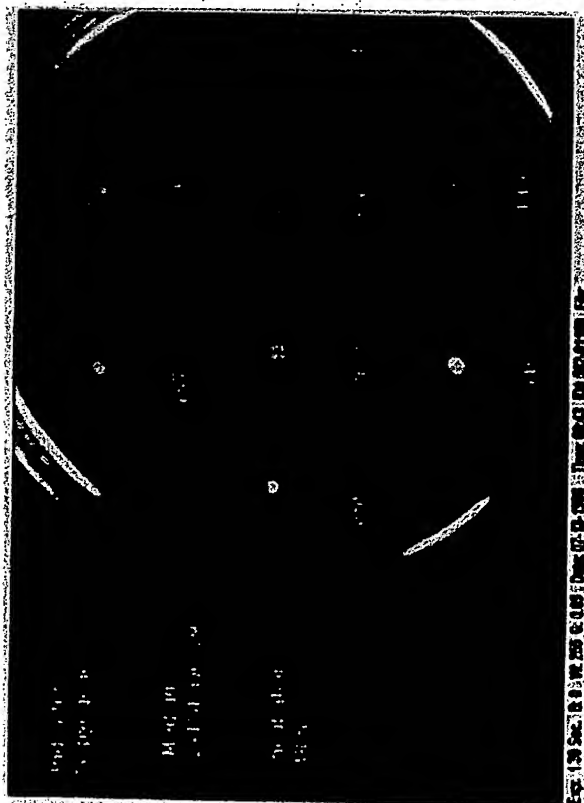
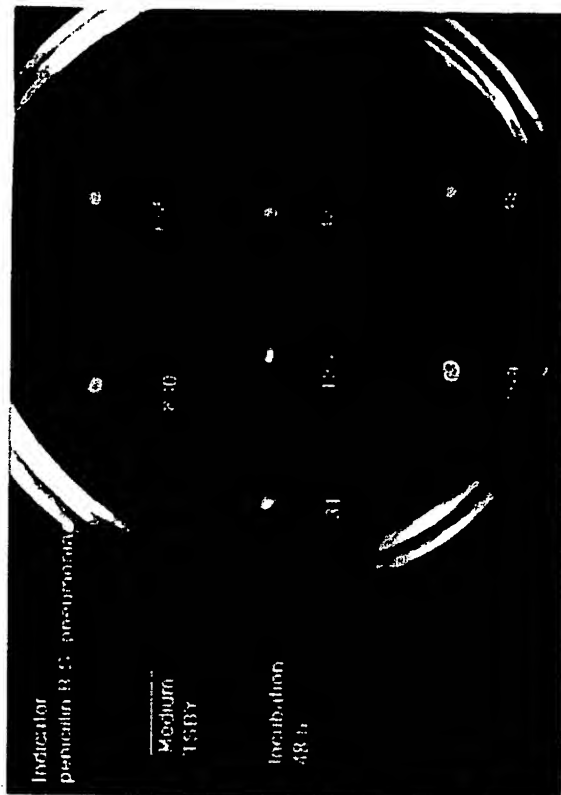
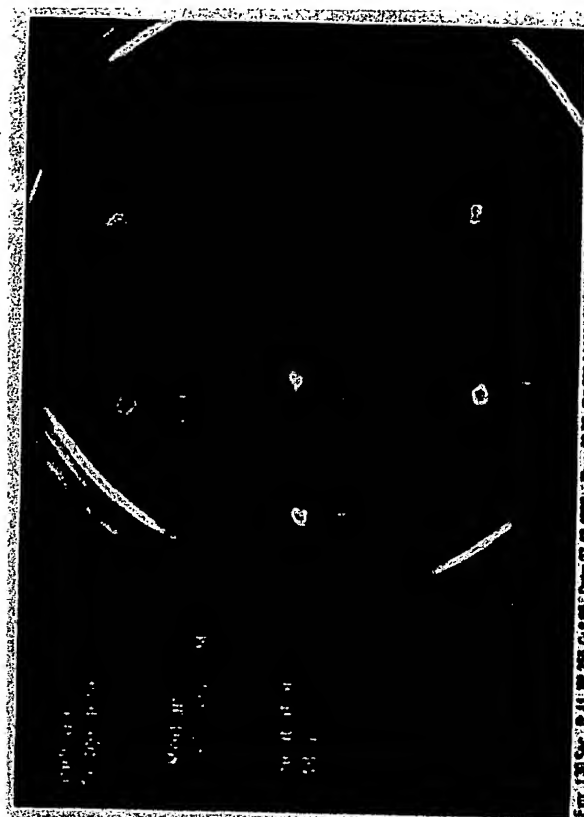
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Antimicrobial Spectrum of Mutacins

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EXHIBIT A
Page 1 of 4

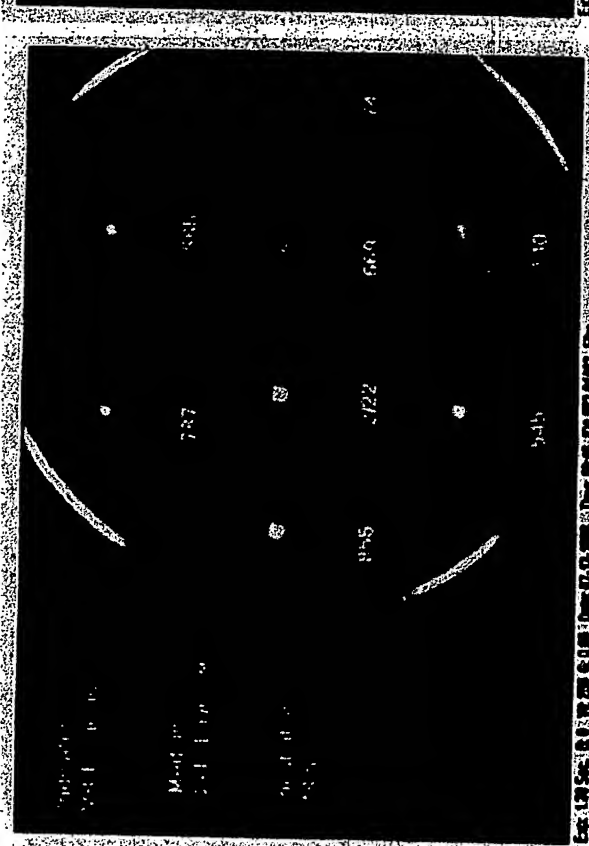
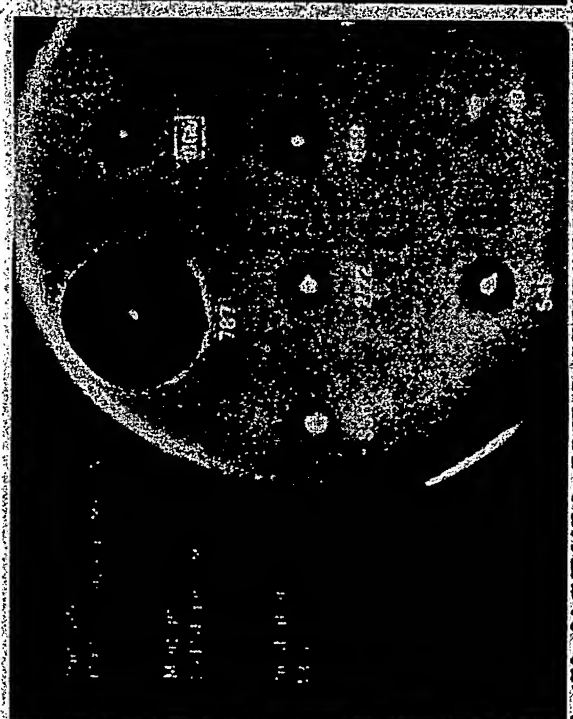
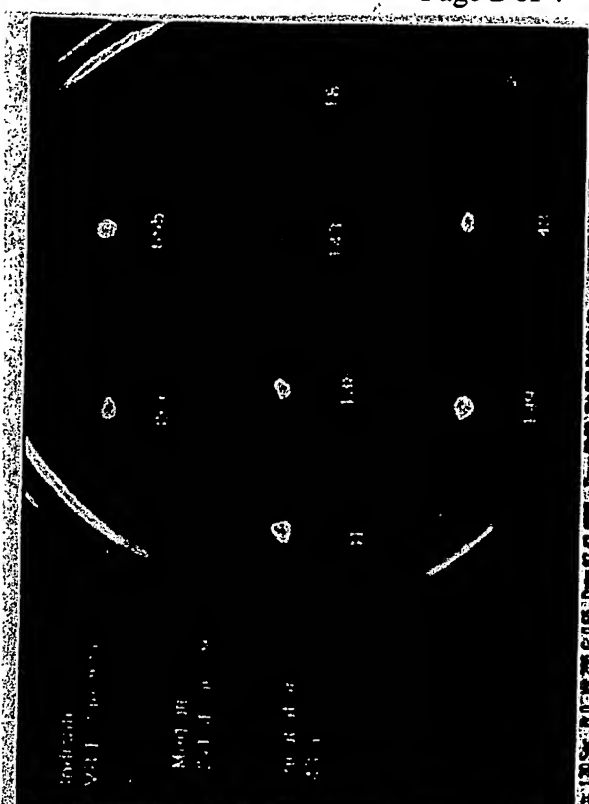
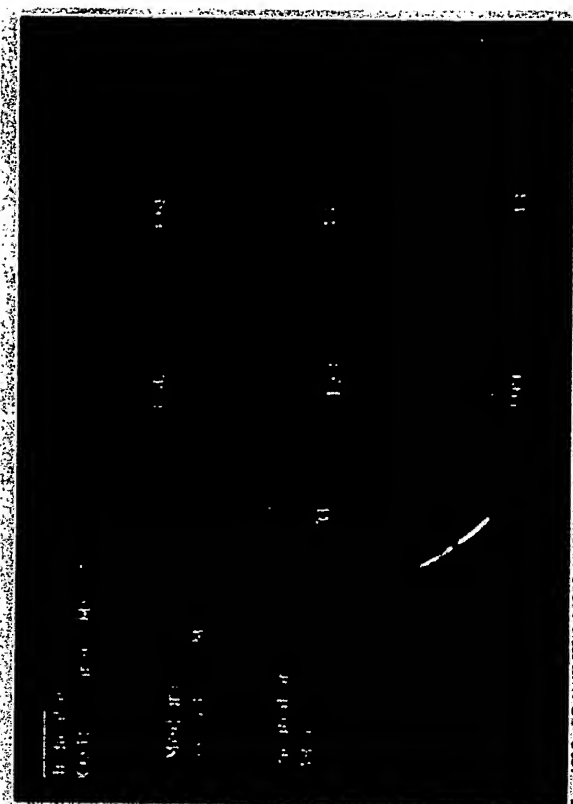


S. pyogenes

S. pneumoniae

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Antimicrobial Spectrum of Mutacins

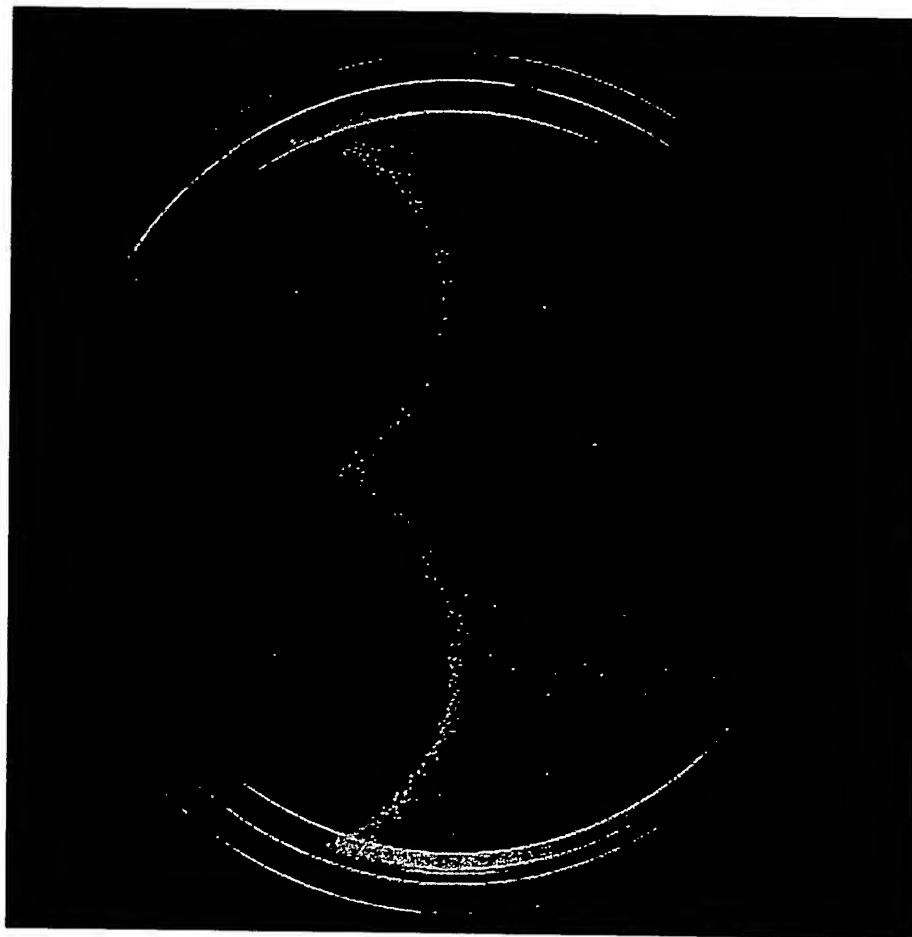


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Mutacin polypeptide antibiotic against *Streptococcus pyogenes*

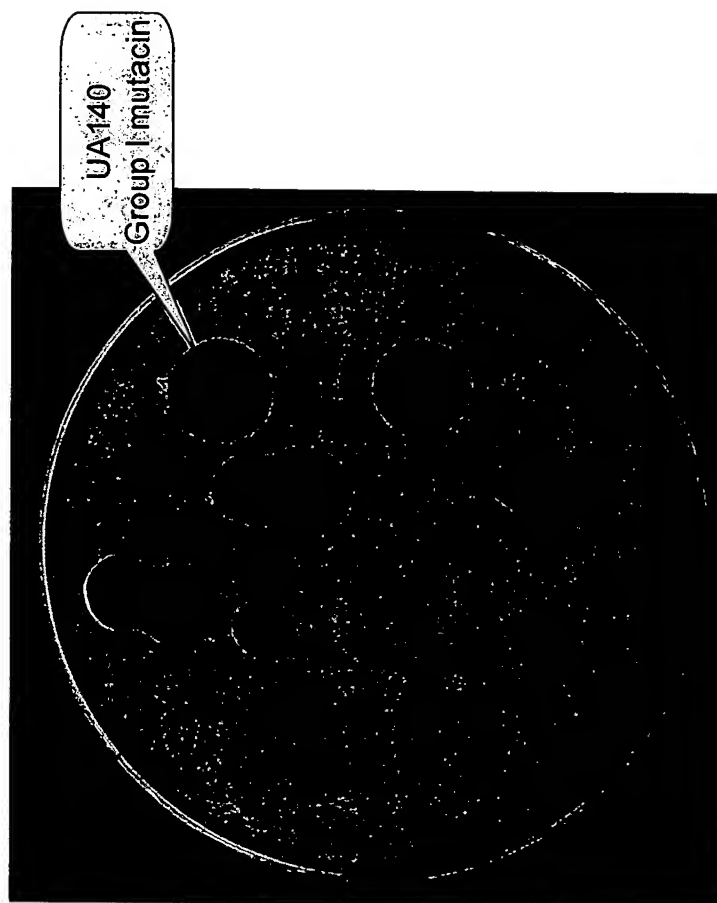


S. pyogenes overlay

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Mutacins against *B. anthracis*

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Semi-purified mutacin I, II, and III spotted on overlay of *B. anthracis* (Sterne)